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1. Environ Health. 2009 Jul 25;8:33.

Controlled human exposures to ambient pollutant particles in susceptible populations.

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Epidemiologic studies have established an association between exposures to air
pollution particles and human mortality and morbidity at concentrations of particles currently found in major metropolitan areas. The adverse effects of pollution particles are most prominent in susceptible subjects, including the elderly and patients with cardiopulmonary diseases. Controlled human exposure studies have been used to confirm the causal relationship between pollution particle exposure and adverse health effects. Earlier studies enrolled mostly young healthy subjects and have largely confirmed the capability of particles to
cause adverse health effects shown in epidemiological studies. In the last few
years, more studies involving susceptible populations have been published. These
recent studies in susceptible populations, however, have shown that the adverse
responses to particles appear diminished in these susceptible subjects compared
to those in healthy subjects. The present paper reviewed and compared control human exposure studies to particles and sought to explain the "unexpected" response to particle exposure in these susceptible populations and make recommendations for future studies. We found that the causes for the discrepant
results are likely multifactorial. Factors such as medications, the disease itself, genetic susceptibility, subject selection bias that is intrinsic to many
controlled exposure studies and nonspecificity of study endpoints may explain part of the results. Future controlled exposure studies should select endpoints
that are more closely related to the pathogenesis of the disease and reflect the
severity of particle-induced health effects in the specific populations under investigation. Future studies should also attempt to control for medications and
genetic susceptibility. Using a different study design, such as exposing subjects
to filtered air and ambient levels of particles, and assessing the

improvement in
biological endpoints during filtered air exposure, may allow the inclusion of higher risk patients who are likely the main contributors to the increased particle-induced health effects in epidemiological studies.

PMCID: 2728708
PMID: 19630984 [PubMed - indexed for MEDLINE]

2. Environ Health. 2009 Apr 16;8:17.

Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies.

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The aim of this review was to assess the evidence from recent prospective studies
that long-term traffic pollution could contribute to the development of asthma-like symptoms and allergic sensitization in children. We have reviewed cohort studies published since 2002 and found in PubMed in Oct 2008. In all, 13
papers based on data from 9 cohorts have evaluated the relationship between traffic exposure and respiratory health. All surveys reported associations with
at least some of the studied respiratory symptoms. The outcome varied, however,
according to the age of the child. Nevertheless, the consistency in the results
indicates that traffic exhaust contributes to the development of respiratory symptoms in healthy children. Potential effects of traffic exhaust on the development of allergic sensitization were only assessed in the four European birth cohorts. Long-term exposure to outdoor air pollutants had no association
with sensitization in ten-year-old schoolchildren in Norway. In contrast, German,
Dutch and Swedish preschool children had an increased risk of sensitization related to traffic exhaust despite fairly similar levels of outdoor air pollution
as in Norway. Traffic-related effects on sensitization could be restricted to individuals with a specific genetic polymorphism. Assessment of gene-environment
interactions on sensitization has so far only been carried out in a subgroup of
the Swedish birth cohort. Further genetic association studies are required and
may identify individuals vulnerable to adverse effects from traffic-related pollutants. Future studies should also evaluate effects of traffic exhaust on the
development and long term outcome of different phenotypes of asthma and wheezing
symptoms.

PMCID: 2674435
PMID: 19371435 [PubMed - indexed for MEDLINE]

3. Hum Genet. 2009 Mar;125(2):119-30. Epub 2008 Dec 27.

Air pollution and mutations in the germline: are humans at risk?

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Genotoxic air pollution is ubiquitous in urban and industrial areas. A variety of
studies has linked human exposure to air pollution with a number of different somatic cell endpoints including cancer. However, the potential for inducing mutations in the human germline remains unclear. Sentinel animal studies of

germline mutations at tandem-repeat loci (specifically minisatellites and expanded simple tandem repeats) have recently provided proof of principle that germline mutations can be induced in vertebrates (birds and mice) by air pollution under ambient conditions. Although humans may also be susceptible to induced germline mutations in polluted areas, uncertainties regarding causative agents, doses, and mutational mechanisms at repetitive DNA loci currently preclude extrapolation from animal data to the evaluation of human risk. Nevertheless, several recent studies have linked air pollution exposure to DNA damage in human sperm, indicating that our germ cells are not impervious to the genotoxic effects of air pollution. Thus, both sentinel animal and human studies have raised the possibility that ambient air pollution may increase human germline mutation rates, especially at repetitive DNA loci. Given that some human genetic conditions appear to be modulated by length mutations at tandem-repeat loci (e.g. HRAS1 cancers, type 1 diabetes, etc.), there is an urgent need for extensive study in this area. Research should be primarily focused upon: (1) the direct measurement of mutation frequencies at repetitive DNA loci in human male germ cells as a function of air pollution exposure, (2) large-scale epidemiology studies of inherited disorders and tandem-repeat associated genetic conditions and air pollution, and (3) the characterization of mutational mechanisms at hypervariable tandem-repeat loci.

PMID: 19112582 [PubMed - indexed for MEDLINE]

4. Mutat Res. 2009 Mar 31;674(1-2):45-54. Epub 2008 Nov 1.

Air pollutants, oxidative stress and human health.

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Air pollutants have, and continue to be, major contributing factors to chronic diseases and mortality, subsequently impacting public health. Chronic diseases include: chronic obstructive pulmonary diseases (COPD), cardiovascular diseases (CVD), asthma, and cancer. Byproducts of oxidative stress found in air pollutants are common initiators or promoters of the damage produced in such chronic diseases. Such air pollutants include: ozone, sulfur oxides, carbon monoxide, nitrogen oxides, and particulate matter. Interaction between oxidative stress byproducts and certain genes within our population may modulate the expression of specific chronic diseases. In this brief review we attempt to provide some insight into what we currently know about the health problems associated with various air pollutants and their relationship in promoting chronic diseases through changes in oxidative stress and modulation of gene expression. Such insight eventually may direct the means for effective public health prevention and treatment of diseases associated with air pollution and treatment of diseases associated with air pollution.

PMID: 19013537 [PubMed - indexed for MEDLINE]

5. Mutat Res. 2009 Mar 31;674(1-2):62-72. Epub 2008 Oct 11.

Inhalation of environmental stressors & chronic inflammation: autoimmunity

and
neurodegeneration.

Gomez-Mejiba SE, Zhai Z, Akram H, Pye QN, Hensley K, Kurien BT, Scofield RH, Ramirez DC.

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Human life expectancy and welfare has decreased because of the increase in environmental stressors in the air. An environmental stressor is a natural or human-made component present in our environment that upon reaching an organic system produces a coordinated response. This response usually involves a modification of the metabolism and physiology of the system. Inhaled environmental stressors damage the airways and lung parenchyma, producing irritation, recruitment of inflammatory cells, and oxidative modification of biomolecules. Oxidatively modified biomolecules, their degradation products, and
adducts with other biomolecules can reach the systemic circulation, and when found in higher concentrations than normal they are considered to be biomarkers
of systemic oxidative stress and inflammation. We classify them as metabolic stressors because they are not inert compounds; indeed, they amplify the inflammatory response by inducing inflammation in the lung and other organs. Thus
the lung is not only the target for environmental stressors, but it is also the
source of a number of metabolic stressors that can induce and worsen pre-existing
chronic inflammation. Metabolic stressors produced in the lung have a number of
effects in tissues other than the lung, such as the brain, and they can also abrogate the mechanisms of immunotolerance. In this review, we discuss recent published evidence that suggests that inflammation in the lung is an important
connection between air pollution and chronic inflammatory diseases such as autoimmunity and neurodegeneration, and we highlight the critical role of metabolic stressors produced in the lung. The understanding of this relationship
between inhaled environmental pollutants and systemic inflammation will help us
to: (1) understand the molecular mechanism of environment-associated diseases,
and (2) find new biomarkers that will help us prevent the exposure of susceptible
individuals and/or design novel therapies.

PMCID: 2676865
PMID: 18977456 [PubMed - indexed for MEDLINE]

6. Mutat Res. 2009 Mar 31;674(1-2):73-84. Epub 2008 Oct 5.

Environmental-induced oxidative stress in neurodegenerative disorders and aging.

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The aetiology of most neurodegenerative disorders is multifactorial and consists
of an interaction between environmental factors and genetic predisposition. Free
radicals derived primarily from molecular oxygen have been implicated and considered as associated risk factors for a variety of human disorders including
neurodegenerative diseases and aging. Damage to tissue biomolecules, including
lipids, proteins and DNA, by free radicals is postulated to contribute importantly to the pathophysiology of oxidative stress. The potential of environmental exposure to metals, air pollution and pesticides as well as diet as

risk factors via the induction of oxidative stress for neurodegenerative diseases
and aging is discussed. The role of genetic background is discussed on the light
of the oxidative stress implication, focusing on both complex neurodegenerative
diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral
sclerosis) and monogenic neurological disorders (Huntington's disease, Ataxia
telangiectasia, Friedreich Ataxia and others). Emphasis is given to role of the
repair mechanisms of oxidative DNA damage in delaying aging and protecting
against neurodegeneration. The emerging interplay between environmental-induced
oxidative stress and epigenetic modifications of critical genes for
neurodegeneration is also discussed.

PMID: 18952194 [PubMed - indexed for MEDLINE]

7. Immunol Allergy Clin North Am. 2008 Aug;28(3):577-88, viii-ix.

Traffic, outdoor air pollution, and asthma.

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The epidemiology of asthma and outdoor air pollution has shown that respiratory
health effects can vary in relation to different emission sources, types of
pollutants, underlying nutritional status, medication use, and genetic
polymorphisms. Using sophisticated exposure assessment methods in conjunction
with clinical tests and biomarkers that provide mechanistic information, the
study of outdoor epidemiology and asthma has evolved into a complex
multidisciplinary field. This article presents an overview of the mechanisms by
which outdoor air pollution and traffic-related emissions lead to changes in
respiratory health and lung function in subjects with asthma.

PMID: 18572108 [PubMed - indexed for MEDLINE]

8. Thorax. 2008 Jun;63(6):555-63.

Genetic susceptibility to the respiratory effects of air pollution.

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There is large variation between individuals in their response to air pollutants.
This review summarises the existing evidence that genetic factors influence the
mechanisms of lung injury caused by air pollutants. Genetic association studies
have compared the adverse effects of air pollutants between subjects with
specific genotypes in biologically relevant genes. In human studies of ozone
exposure, polymorphisms in oxidative stress genes (NQO1, GSTM1, GSTP1) modify
respiratory symptoms, lung function, biomarkers and risk of asthma. Inflammatory
gene polymorphisms (TNF) influence the lung function response to ozone, and the
effect of different levels of ozone on the development of asthma. Polymorphisms
in oxidative stress genes (GSTM1, GSTP1) alter the response to combined exposure
to ragweed pollen and diesel exhaust particles. Importantly, polymorphisms in an

oxidative stress gene (GSTM1) have predicted patients with asthma who benefit from antioxidant supplementation in Mexico City, which has chronically high ozone exposure. Genetic linkage studies of families have not been feasible for studying the effects of air pollution in humans, but some progress has been made with pedigrees of specially bred mice, in identifying chromosomal regions linked to effects of ozone or particles. A high priority now, in addition to avoiding exposure in the most susceptible people, is to clearly identify the most effective and safe chemopreventive agents for individuals who are genetically susceptible to the adverse effects of air pollution (eg, antioxidants to be taken during high ozone levels).

PMID: 18511640 [PubMed - indexed for MEDLINE]

9. Curr Allergy Asthma Rep. 2008 Apr;8(2):139-46.

The effect of air pollution on asthma and allergy.

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Air pollution exposure is associated with increased asthma and allergy morbidity and is a suspected contributor to the increasing prevalence of allergic conditions. Observational studies continue to strengthen the association between air pollution and allergic respiratory disease, whereas recent mechanistic studies have defined the prominent role of oxidative stress in the proallergic immunologic effects of particulate and gaseous pollutants. The identification of common genetic polymorphisms in key cytoprotective responses to oxidative stress has highlighted the importance of individual host susceptibility to pollutant-induced inflammation. Future therapy to reduce the adverse effects of air pollution on allergic respiratory disease will likely depend on targeting susceptible populations for treatment that reduces oxidative stress, potentially through enhancement of phase 2 enzymes or other antioxidant defenses.

PMID: 18417056 [PubMed - indexed for MEDLINE]

10. Proc Am Thorac Soc. 2007 Jul;4(3):217-20.

Gene-air pollution interactions in asthma.

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Genetic and environmental factors interact to cause asthma. However, genetic studies have generally ignored environmental factors and environmental studies have generally ignored genetics. Thus, there are few examples from the literature of specific gene-environment interactions in relation to asthma. The clearest examples of genetic interactions for inhaled pollutants exist for endotoxin, environmental tobacco smoke, and ozone. Endotoxin-genetic interactions in asthma are the focus of two other manuscripts from this conference, so this review focuses on environmental tobacco smoke and ozone. In the sparse literature, there is evidence for the role of specific genes involved in oxidative stress,

notably
GSTM1 and TNF, in the respiratory responses to ozone and environmental tobacco
smoke. There are few data on genes involved in innate immune pathways, which are
crucial in response to endotoxin and may play a role in response to ozone and
environmental tobacco smoke. Genes involved in oxidative stress may interact with
both air pollutants and diet in relation to asthma phenotypes. Future directions
to advance the field include whole genome association studies, better assessment
of exposure and phenotypes, and consideration of joint interactions with diet and
other co-factors that influence individual susceptibility.

PMCID: 2647621
PMID: 17607002 [PubMed - indexed for MEDLINE]

11. Pharmacol Ther. 2007 May;114(2):129-45. Epub 2007 Feb 24.

Environmental factors and developmental outcomes in the lung.

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The developing lung is highly susceptible to damage from exposure to
environmental toxicants particularly due to the protracted maturation of the
respiratory system, extending from the embryonic phase of development in utero
through to adolescence. The functional organization of the lungs requires a
coordinated ontogeny of critical developmental processes that include branching
morphogenesis, cellular differentiation and proliferation, alveolarization, and
maturation of the pulmonary immune, vasculature, and neural systems. Therefore,
exposure to environmental pollutants during crucial periods of prenatal and/or
postnatal development may determine the course of lung morphogenesis and
maturation. Depending on the timing of exposure and pathobiological response of
the affected tissue, exposure to environmental pollutants can potentially result
in long-term alterations that affect the structure and function of the
respiratory system. Besides an immature respiratory system at birth, children
possess unique differences in their physiology and behavioral characteristics
compared to adults that are believed to augment the vulnerability of their
developing lungs to perturbations by environmental toxins. Furthermore, an
interaction between genetic predisposition and increased opportunity for exposure
to chemical and infectious disease increase the hazards and risks for infants and
children. In this article, the evidence for perturbations of lung developmental
processes by key ambient pollutants (environmental tobacco smoke [ETS], ozone,
and particulate matter [PM]) are discussed in terms of biological factors that
are intrinsic to infants and children and that influence exposure-related lung
development and respiratory outcomes.

PMID: 17408750 [PubMed - indexed for MEDLINE]

12. Curr Opin Allergy Clin Immunol. 2007 Feb;7(1):75-82.

Gene-environmental interaction in asthma.

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PURPOSE OF REVIEW: Asthma is likely to result from the effects of environmental stimuli in genetically susceptible individuals. This review summarizes recent studies of gene-environmental interaction in the pathogenesis of asthma, focusing on study designs. RECENT FINDINGS: Studies using genetic epidemiology, in-vitro and ex-vivo models and in-vivo model organisms demonstrate that gene-environmental interaction in involved in the development of asthma. Genetic association studies show a reduced risk of asthma and atopy with early life exposure to farming environments and house dust endotoxin, and increased risk with environmental tobacco smoke. These associations are modified by CD14 genotype. In people with a specific genotype, high environmental exposure may have the opposite effect of low exposure, possibly explaining some of the inconsistencies in previous studies. In-vitro and ex-vivo cell culture experiments show gene-environmental interactions with Toll-like receptor agonists, viruses and tobacco smoke. Interactions between innate immunity genes and exposure to endotoxin and air pollution have been observed in in-vivo mouse models. SUMMARY: The expanding evidence for gene-environmental interaction in asthma indicates the importance of measuring environmental factors in genetic studies of asthma. Understanding gene-environmental interaction would facilitate risk prognostication, improve preventive strategies and develop targeted interventions in people with asthma.

PMID: 17218815 [PubMed - indexed for MEDLINE]

13. Curr Opin Pulm Med. 2007 Jan;13(1):63-6.

Asthma and air quality.

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PURPOSE OF REVIEW: There is evidence for an association between asthma and air pollutants, including ozone, NO2 and particulate matter. Since these pollutants are ubiquitous in the urban atmosphere and typically correlated with each other it has been difficult to ascertain the specific sources of air pollution responsible for the observed effects. Similarly, uncertainty in determining a causal agent, or multiple agents, has complicated efforts to identify the mechanisms involved in pollution-mediated asthma events and whether air pollution may cause asthma as well as exacerbate preexisting cases. RECENT FINDINGS: Numerous studies have examined specific sources of air pollution and their relationship to asthma. This review summarizes recent work conducted, specifically, on traffic pollution and presents results that elucidate several plausible biological mechanisms for the observed effects. Of note are studies linking susceptibility to several genetic polymorphisms. Together, these studies suggest that remaining uncertainties in the asthma-air pollution association may be addressed through enhanced assessment of both exposures and outcomes. SUMMARY: Air-pollution research is evolving rapidly; in the near future, clinicians and public health agencies may be able to use this new information to provide recommendations for asthmatics that go beyond only paying attention to the air-pollution forecast.

PMID: 17133127 [PubMed - indexed for MEDLINE]

14. Environ Health Perspect. 2006 Apr;114(4):627-33.

How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma.

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Asthma is a multifactorial airway disease that arises from a relatively common genetic background interphased with exposures to allergens and airborne irritants. The rapid rise in asthma over the past three decades in Western societies has been attributed to numerous diverse factors, including increased awareness of the disease, altered lifestyle and activity patterns, and ill-defined changes in environmental exposures. It is well accepted that persons with asthma are more sensitive than persons without asthma to air pollutants such as cigarette smoke, traffic emissions, and photochemical smog components. It has also been demonstrated that exposure to a mix of allergens and irritants can at times promote the development phase (induction) of the disease. Experimental evidence suggests that complex organic molecules from diesel exhaust may act as allergic adjuvants through the production of oxidative stress in airway cells. It also seems that climate change is increasing the abundance of aeroallergens such as pollen, which may result in greater incidence or severity of allergic diseases. In this review we illustrate how environmental tobacco smoke, outdoor air pollution, and climate change may act as environmental risk factors for the development of asthma and provide mechanistic explanations for how some of these effects can occur.

PMCID: 1440792
PMID: 16581557 [PubMed - indexed for MEDLINE]

15. J Occup Environ Med. 2005 Dec;47(12):1285-91.

Asthma, genes, and air pollution.

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OBJECTIVE: The objective of this article is to evaluate genetic risks associated with the pulmonary response to air pollutants, including particulates and ozone.
METHODS: A comprehensive review of articles related to the genetics of asthma with particular attention to air pollution was conducted through a search of the National Library of Medicine's PubMed database. RESULTS: Asthma, which affects over 15 million people in the United States, is characterized by inflammation leading to reversible airflow obstruction. Triggered by exposure to numerous occupational and environmental agents, asthma has long been considered to occur more frequently in families, with upwards of a 50% higher rate in the offspring of parents with asthma. Asthma genetic studies have used two major methods: mapping techniques that pinpoint gene loci and studies that identify genes and polymorphisms associated with various asthma mechanisms such as inflammatory mediators. The most consistently replicated chromosomal regions associated with

asthma have been chromosomes 2q, 5q, 6p, 12 q, and 13q. Because the formation of reactive oxygen species is a major aspect of the inflammatory process of asthma, genetic aberrations associated with antioxidants such as glutathione S-transferase (GST) may shed light on reasons why some people with asthma seem more at risk of exacerbations as a result of air pollution. People with a polymorphism at the GSTP 1 locus, which codes for GST, one of a family of pulmonary antioxidants, have higher rates of asthma. Children in Mexico City with the GSTM1 null genotype demonstrated significant ozone-related decrements in lung function. Animal studies support the key role of antioxidants in reducing the inflammatory response associated with exposure to diesel exhaust particles. CONCLUSIONS: Oxidative stress is a key mechanism underlying the toxic effects of exposure to some types of air pollution. Asthmatics with the null genotype for the antioxidant, GST, seem more at risk of the pulmonary effects of air pollution.

PMID: 16340710 [PubMed - indexed for MEDLINE]